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Sir John and Lady Rita Cornforth: a distinguished chemical partnership

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ABSTRACT

This review describes the life of Sir John Cornforth AC CBE FRS, who was awarded the Nobel Prize for Chemistry in 1975. It covers his early life in Australia, his work in Oxford, the National Institute for Medical Research, the Milstead Laboratory of Chemical Enzymology and the University of Sussex, together with the contributions made by his wife, Lady Rita Cornforth.

Keywords: *Sir John Cornforth, Kappa, Lady Rita Cornforth, Nobel Prize, deafness, biosynthesis, stereochemistry*

Sir John and Lady Cornforth

"For the scientist, truth is seldom the sudden light that shows new order and beauty; more often, truth is the uncharted rock that sinks his ship in the dark."

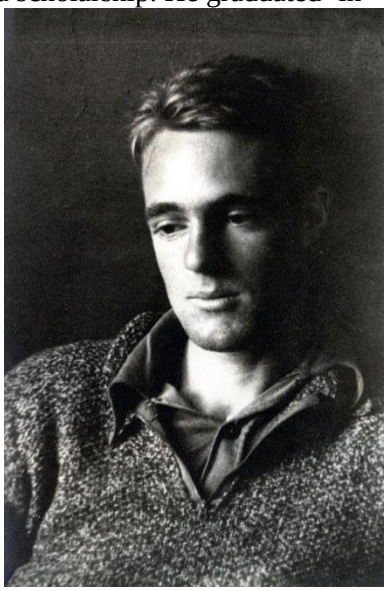
Sir John Cornforth, 1993

Sir John Cornforth AC CBE FRS was one of the major figures of organic chemistry of the 20th century. His pioneering work on the stereochemistry of enzyme reactions was acknowledged by the award of the Nobel Prize for Chemistry in 1975. He also made significant contributions to the synthesis of sterols, the structure and chemistry of penicillin and the chemistry of oxazoles. Throughout his career he was supported by his wife, Lady Rita Cornforth who was herself an excellent chemist.

John Warcup Cornforth was born in Sydney, Australia on the 7 September 1917. His father was born in Bristol and was an Oxford graduate who had emigrated to Australia and who taught classics. His mother (née Eipper) had been born in Australia and was of German and Irish descent. She had been a nurse before she married. Cornforth was the second of four children. Part of his childhood was spent in rural New South Wales in Armidale. By the age of 10 he had started to suffer from the first signs of deafness caused by a progressive hereditary disease, otosclerosis, which was accompanied by tinnitus. It developed to the extent that his deafness was complete in his late teens. By the time that he reached secondary school age, the family had returned to Sydney and Cornforth attended Sydney Boys High School.

Deafness limited Cornforth's choice of subject. At one time he had thought of becoming a barrister. However, an inspirational chemistry teacher, Laurence Basser, encouraged him to study chemistry. By the age of 14, he had built himself his own laboratory at home. The innovative practical skills which he developed in this way were to stand him in good stead in later life. Astronomy was another hobby and he built his own telescope. It was on walks in the bush and the Blue Mountains, where Cornforth contemplated the diversity of Australian plants, that he became attracted to the study of natural products.

Cornforth entered the University of Sydney at the early age of 16 with a scholarship. He graduated in 1937 with first class honours in chemistry and with the university prize. His deafness had meant that he was unable to hear the lectures and so he learned his chemistry by reading not only the textbooks but also the original literature. Since a substantial part of the latter was in German, he taught himself the language. He developed a critical reading of the scientific literature, which was invaluable to him throughout his career. Cornforth had an extraordinarily good memory and he could recall, often many years later, crucial observations which had been reported in the literature. It was at this stage that he acquired the nickname 'Kappa' which remained with him throughout his life. It came from the Greek letter κ. The initials JC when elided become a Greek κ. He engraved his laboratory glassware with a κ to prevent it being 'borrowed' by other students.



Portrait of a young man

During his MSc research he met Rita Harradence who was later to become his wife. She was born in Sydney in 1915 and had been educated at St George's Girls High School where her interest in chemistry had been stimulated by another exceptional teacher, Lilian Whiteoak. She was awarded the top state scholarship from New South Wales to study chemistry at the University of Sydney. She was the year ahead of Cornforth and graduated with the top first class honours degree in chemistry in 1936. She shared the University prize for that year with another eminent Australian chemist, Arthur Birch. The story of Rita's first meeting with her future husband is that Cornforth, using the glass-blowing skills which he had developed in his home laboratory, was able to repair a broken Claisen flask of hers.

There is an interesting opening to their first joint paper based on their honours degree research and published in 1938. It begins: 'Robinson and Robinson (*J. Chem. Soc.*, 1918, 639) have discussed the conditions necessary for the success of Fischer's indole synthesis...' Sir Robert Robinson (1886–1975) carried out a substantial amount of research in collaboration with his wife and was awarded the Nobel Prize in 1947. He was also to become their supervisor in Oxford and had, for a short period (1913–1915), been Professor of Chemistry at the University of Sydney.

The two young chemists heading to Britain from Australia

In the 1930s, Australian universities did not offer the PhD degree and so, in 1939, John Cornforth and Rita Harradence obtained prestigious 1851 Exhibition Scholarships to travel to Oxford to undertake their doctoral research. They sailed from Sydney on 12 August l939 on board the Orient Line, Orama. Because of the outbreak of the Second World War on 3 September 1939, the liner was diverted *via* Cape Town where they had to make the decision as to whether to return to Australia or continue. The rest is history.

They began their research in the Dyson Perrins Laboratory in Oxford on the synthesis of sterols under the supervision of Robert Robinson. Rita

The two young chemists heading to Britain from Australia

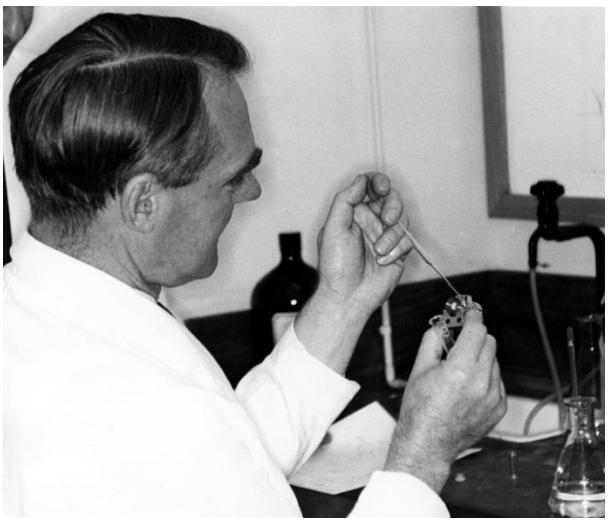
Harradence was a member of Somerville College and John Cornforth of St Catherine's College. They completed their D.Phil. degrees in 1941 and were married in that year. Cornforth's early work on the synthesis of sterols was characterised not only by careful experimental and observational skills but also by a thorough command of the literature and interpretation of the results enabling him to make significant progress in his synthetic work. After some research on anti-malarial quinolines, they joined the Oxford penicillin team in the summer of 1943. The structure of penicillin was unknown at the time but its antibiotic properties had made it a subject of great importance in the war effort. Cornforth's synthesis of penicillamine, a degradation product of penicillin, established the structure of part of the penicillin core structure.

Because of the war-time restrictions much of this work was only described in the confidential Medical Research Council 'Committee on Penicillin Synthesis' reports and not published in the conventional scientific literature. A book, *The Chemistry of Penicillin*, to which Cornforth made significant contributions, appeared in 1949.

In 1946, the Cornforths moved to the National Institute for Medical Research (NIMR) in Hampstead and then to the new NIMR building at Mill Hill, London. Here the Director, Sir Charles Harington, allowed Cornforth to complete his work on sterol synthesis which was published in 1951. The Cornforths also explored facets of oxazole chemistry which had been started in Oxford during their work on penicillin. They not only developed a novel oxazole synthesis but also uncovered a mechanistically interesting rearrangement which has subsequently become known as the Cornforth rearrangement.

The post-war period was a time when a number of research institutes were established to facilitate inter-disciplinary research and were funded on different models to the present. Consequently, the Cornforths were able to establish collaborations with medical biochemists on a wide range of topics including anti-tubercular drugs, biologically-active plant constituents, tryptophan metabolites and neuraminic acids.

The most fruitful collaboration was with a lipid biochemist, George Popják (1914–1998), on the biosynthesis of squalene and cholesterol from acetate and mevalonic acid units. This collaboration, in which Popják carried out the biochemical work, continued when Popják moved to the Medical Research Council Experimental Radiopathology Research Unit at Hammersmith Hospital, London. In 1948, a paper by A.G. Ogston had a profound influence on Cornforth's thinking on the stereochemistry of enzyme reactions. Ogston pointed out that when a compound Caabc has a three-point attachment to a chiral enzyme, the two chemically identical groups 'a' lose their identity and are distinguishable as far as the enzyme is concerned and are pro-chiral.
Cornforth applied this concept to his work in elucidating the stereochemistry of enzyme reactions by using substrates in which hydrogen atoms were stereospecifically labelled with deuterium or tritium. Rita Cornforth carried out a number of the syntheses of stereospecifically labelled mevalonates which were required for the work on farnesyl diphosphate, squalene and cholesterol biosynthesis.



Sir John at work

In 1962, at the instigation of Lord Rothschild and Sir Robert Robinson, Shell Ltd. established the Milstead Laboratory of Chemical Enzymology at Sittingbourne in Kent with Cornforth and Popják as co-directors. These laboratories were known colloquially as the 'PopCorn' labs. This appointment

enabled Cornforth to continue the collaboration on the elucidation of the stereochemistry of the enzyme reactions involved in the conversion of the terpenoid precursor, mevalonic acid, into squalene and cholesterol. Cornforth had identified 14 steps between mevalonic acid and squalene where there were two stereochemically distinct possibilities. His studies enabled him to identify which one of the 2^{14} (16,384) biosynthetic pathways was involved.

After Popják moved to the University of California, Los Angeles in 1968, Cornforth began work with the European biochemist Professor Hermann Eggerer (1927–2006) from the Institut für Biochemie der Universität München. This particular collaboration involved the elucidation of the stereochemistry of enzyme reactions using a chiral methyl group in which two of the hydrogen atoms were stereospecifically replaced with deuterium and tritium respectively. The methodology was initially developed in order to determine the stereochemistry of the addition of a proton to an alkene to form a methyl group in the conversion of isopentenyl diphosphate to dimethylallyl diphosphate. Subsequently, the methodology was used to explore the enzyme reactions involving the utilisation and formation of acetyl co-enzyme A, and to establish whether these enzyme reactions proceeded with inversion or retention of configuration. This provided a valuable insight into the stereochemistry of the reactions of the citric acid cycle and fatty acid biosynthesis which are central pathways in primary metabolism. This work not only involved developing a synthesis of chiral acetate but also of methods to assess its chirality. Cornforth was awarded the Nobel Prize in 1975 for his work on the stereochemistry of enzyme reactions jointly with a Yugoslav–Swiss chemist, Vladimir Prelog (1906–1998).

Apart from his biosynthetic experiments, Cornforth completed a number of syntheses during this period. In the context of work on the synthesis of squalene, he developed a novel stereospecific method for making a trisubstituted double bond. This was based on a mechanistic model for the stereochemistry of nucleophilic addition to a carbonyl group which has become known as the Cornforth model. Another group of studies involved the synthesis of the plant dormancy hormone, abscisic acid.

Throughout his time in Oxford, at the NIMR and at Milstead, Rita Cornforth had played an immensely valuable supportive role both in carrying out many of the syntheses of the labelled compounds and in acting as Cornforth's 'ears' at scientific meetings. They collaborated in over 41 publications. He acknowledged this support in his Nobel Prize speech:

"She has eased for me beyond measure the difficulties of communication that accompany deafness; her encouragement and fortitude have been my strongest support."

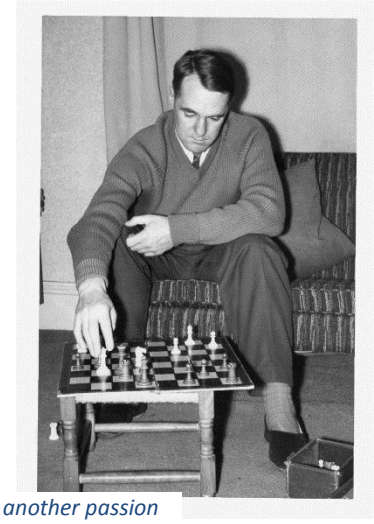
In the spring of 1975, Cornforth moved to the University of Sussex as a Royal Society Research Professor. At Sussex, he continued a project, which he and Rita had started at Shell, on the synthesis of a compound which might mimic the catalytic activity of an enzyme system in hydrating an alkene. This involved innovative syntheses of some substituted dibenzophospholes and included the development of a copper-based aryl coupling reaction to form diphenyls. This pre-dated the organometallic methods based on palladium chemistry. He collaborated with a small group of post-doctoral fellows, mainly from Australia, and although he managed to establish a limited 'proof of concept', the work was severely hampered by lack of funds. Cornforth continued to lecture including to undergraduates and to supervise project students, until he was well into his eighties. The companionship of the laboratory provided considerable comfort to him in overcoming the isolation brought about by his deafness. Cornforth had worked at the bench throughout his scientific career and he was able to bring many years of laboratory experience together with technical and observational skills to his research and teaching. However, financial problems within the university meant that he had to retire from active chemistry in 2005.

Cornforth was given many honours, medals, honorary degrees and lectureships during his career and his

The Cornforth family at Sir John's investiture at Buckingham Palace

acceptance speeches for these contained revealing insights into his scientific method. He was made a CBE in 1972 and given a knighthood in 1977. He was named the Australian of The Year in 1975 and made a Companion of the Order of Australia (AC) in 1991. He was elected a Fellow of the Royal Society in 1953. His scientific awards included the Corday- Morgan (1953) and the Flintoff (1966) medals of the Royal Society of Chemistry, the Davy (1968) and the Copley (1982) medals of the Royal Society, the Stouffer prize (1967) , the Ernest Guenther award (1969) and the Prix Roussel (1972).

Cornforth was an excellent chess player having been junior champion of New South Wales at the age of 15. There was often a chess board in the laboratory tea room. Although the pleasure of music was denied to him, he derived a great deal of enjoyment from poetry and he could recite many poems at length particularly the work of W.B. Yeats. He was active in playing tennis, in gardening and walking. The large garden of his home in Lewes was carefully tended and contained many fruit bushes.



Playing chess was another passion

Lady Rita Cornforth died on 6 November 2012 aged 97 after a long illness throughout which Sir John Cornforth had cared for her. Sir John Cornforth himself died on 8 December 2013 aged 96 after a stroke. They are survived by a son, two daughters, grandchildren and great-grandchildren.

There are a number of conclusions that can be drawn from this review. Firstly, although deafness is a terrible handicap, it can be overcome with exceptional perseverance. Secondly, stimulating teaching and practical experience in a chemist's formative years are extremely important. Thirdly, the time-scale involved in the development of specialist skills and collaborations for effective, particularly inter-disciplinary, long-term research are very different from the conventional time-scale of current research grants. It is worth noting the extent to which Cornforth's later work was hampered by financial constraints.

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